Specialty Conference

The Neurologic Sequelae of Cardiac Arrest

Discussant
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This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. Taken from a transcription, it has been edited by Drs Paul G. Ramsey, Associate Professor of Medicine, and Philip J. Fialkow, Professor and Chair of the Department of Medicine.

W. T. LONGSTRETH, JR, MD:* After trauma and drug overdose, cardiac arrest is the third most common cause of coma in Seattle. Just 20 to 30 years ago, all persons experiencing a cardiac arrest died. Because of technologic developments,[1] patients may now survive but may also suffer brain damage. In this conference I review information concerning the neurologic sequelae of cardiac arrest, concentrating on investigations done at the University of Washington and on Medic I, the prehospital emergency medical system in Seattle. I review the clinical course, prognosis and treatment of coma after cardiac arrest. The discussion of the clinical course and prognosis encompasses both early prognostic factors, including blood glucose level, and later prognostic factors, including cerebrospinal fluid creatine kinase. An important use of the information gained from these studies on complete, global brain ischemia is its possible application to patients with focal brain ischemia. In further discussing this topic, I will focus on decisions that clinicians face concerning limiting medical support.

Clinical Course and Prognosis

The Early Course and Prognosis

Our study population consisted of 459 patients who had suffered out-of-hospital cardiac arrests in Seattle between March 1970 and March 1980, had been resuscitated by Medic I and had been admitted to Harborview Medical Center.[2] Patients who experienced cardiac arrest in a hospital setting were excluded because of a possible difficulty in determining the neurologic outcome specific to the arrest. The major outcome of interest was whether a patient regained consciousness or awakened, as defined by chart documentation of the patient's ability to follow commands or speak comprehensibly. Only patients with well-documented ventricular fibrillation or asystole were considered. Patients in whom cardiac arrest had followed another event, such as respiratory arrest, drug overdose or trauma, that might confound the determination of outcome were excluded. Complete follow-up was obtained for almost all patients.

Overall, 39% of the patients never awakened after cardiac arrest. In these patients, brain death was a rare outcome probably reflecting a greater resistance of the brain than the heart to such insults. Most of the patients who never awakened entered a persistent vegetative state.[3] Of these patients, 80% died during their initial hospital stay. The patient surviving longest in a vegetative state lived more than five years before his final cardiac arrest. Karen Ann Quinlan recently died after about ten years in a persistent vegetative state ("A Long Twilight Comes to an End [Karen Ann Quinlan, Obituary]," *Newsweek,* June 24, 1985, p 81), and a 6-year-old girl who never awoke after her appendectomy survived for 37 years, 111 days.[4]

Of the 61% of our patients who did awake, two thirds had complete neurologic recovery. To identify factors that predict outcome, 27 variables available from the time of admission were examined.[5] Although most of them were significantly related to awakening, none considered alone was pathognomonic. Consequently, we used a multivariable predictive rule.[6] With discriminant analysis, 7 of the 27 variables were found to be significantly related to awakening. After examining several models for complexity and efficiency, we decided on a four-variable rule (motor response, pupillary light response, spontaneous eye movements and admission blood glucose) (Table 1). When these four variables were controlled, the only other items significantly related to awakening were whether the arrest had been witnessed, whether epinephrine had been given during the resuscitation and whether norepinephrine had been given. When all patients not awake on admission after an out-of-hospital cardiac arrest were classified, the potential scores ranged from 0 to 9, and the percentage of patients who awoke varied from 0% to 95% (Table 2).

Other investigators have also examined multivariable predictive rules. In a cooperative study on nontraumatic coma,[7] the subgroup of patients with hypoxic-ischemic coma lasting six hours or more was analyzed.[8] A multivariable technique, recursive partitioning, was used to generate predictions of neurologic outcome at various times after cardiac arrest. This prospective study included a mix of patients with in-hospital and out-of-hospital cardiac arrests and other hypoxic and ischemic brain insults. Despite the different patient population, the initial prediction rule identified the major predictor variables as pupillary light response, motor response and spontaneous eye movements.[8] Thus, both models found similar early clinical predictors of neurologic outcome. Neither predictive rule, however, has been validated in a prospective setting.

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ABBREVIATIONS USED IN TEXT
CK = creatine kinase
CSF = cerebrospinal fluid

Admission Blood Glucose

The importance of the admission blood glucose level as a predictor of neurologic recovery after cardiac arrest deserves further comment. In 1977 Myers and Yamaguchi produced 13 minutes of complete, global brain ischemia with ventricular fibrillation in monkeys.[9] After resuscitation, minimal brain damage was found in all but two animals that showed extensive cortical necrosis. The only difference in protocol was that the two monkeys with severely damaged brains had been given 200 ml of 5% dextrose solution before the arrest and the others had received a saline solution. The importance of the blood glucose level as a determinant of brain damage at the time of a hypoxic-ischemic brain insult has also been shown in animals by other investigators.[10-15] The mechanism for this augmented damage is unknown but may be associated with excessive lactic acid production.[16] When blood stops flowing, glucose metabolism continues anaerobically, and the availability of more glucose at the time of stagnation can cause a greater production of lactic acid. How lactic acid can be linked to cell destruction is unknown but may involve the flux of calcium into the cell.[17,18]

Further evidence for glucose as a predictor of neurologic recovery was found in studies done in patients with focal brain ischemia or ischemic stroke. A direct association has been found between a fasting blood glucose level within 48 hours of admission and severity of the acute stroke as measured by clinical examination and computed tomographic scans of the head.[19] Other investigators have shown that the blood glucose level within 24 hours of admission is significantly related to the percentage of patients who never regain independence.[20]

Whether an elevated glucose level is a cause or an effect of brain damage is an important question raised by the findings in patients after cardiac arrest and ischemic stroke. In an attempt to answer this question, we examined data that had been collected for another study. Serial blood specimens were collected on patients during out-of-hospital cardiac resuscitation mostly in 1977.[21] These data showed that the blood glucose level rose significantly during the resuscitation of patients who died in the field and of those who were admitted and either awakened or never awakened. With the time variable controlled in the analysis, the blood glucose level and awakening state were not significantly related. Unfortunately, the admission blood glucose level in these patients was unknown. Using the duration of cardiopulmonary resuscitation and regression lines summarizing these data, however, the mean blood glucose level at the end of resuscitation was estimated to be 254 mg per dl for those who awakened and 309 mg per dl for those who never awakened. These estimates were similar to actual blood glucose levels found on admission in a previous study: 262 mg per dl for those who awakened and 341 mg per dl for those who never awakened.[22] Thus, the higher blood glucose level on admission in patients who never awaken may simply reflect a longer and more stressful resuscitation. These data do not suggest that lowering blood glucose levels during or after admission would alter the outcome.

Interactions among blood glucose level, duration and ease of resuscitation and outcome remain difficult to examine in patients. Further experiments in animals are needed. Until issues of cause and effect are resolved, however, glucose loading should probably be avoided in patients with or at risk for hypoxic-ischemic brain damage.[14,23]

TABLE 1.—*Rule to Calculate Score That Predicts Awakening**†

Motor Response	+	*Pupillary Light Response*	+	*Spontaneous Eye Movements*	+	*Blood Glucose Level on Admission, mg/dl*
0=Absent		0=Absent		0=Absent		0=≥300
1=Extensor posturing		3=Present		1=Present		1=<300
2=Flexor posturing						
3=Nonposturing						
4=Withdrawal or localizing						

*Modified from Longstreth et al.[5]
†See Table 2 to interpret score.

Later Course and Prognosis

The results from the studies at the University of Washington suggest that the probability of awaking after cardiac arrest falls precipitously during the first four days after arrest (Table 3). Of the 459 patients studied, 279 awakened eventually, giving an overall probability of awaking of .61. By four days after the arrest, however, the probability of awaking was only .14. The population available for awakening was continually being reduced due to patients who awoke or died without awakening. Because deaths occurred more frequently than awakenings after day 4, the probability for awakening actually rose. The last three patients to awaken in this series did so at 56, 75 and 100 days after cardiac arrest.

The degree of neurologic recovery in patients who awakened also varied considerably during the first four days after arrest (Table 4). Of the 279 patients who awakened eventually, the probability for full recovery was .67. The probability of full recovery fell, however, so that after four days, all 14 patients who awakened had some permanent deficits and all six patients who awakened after 14 days had severe permanent deficits that precluded independent living.

These findings may be used to predict neurologic recovery at a particular time after an out-of-hospital cardiac arrest. For example, 142 patients were not awake two days after cardiac arrest and 39 (27%) of those patients eventually awakened (Table 3). Of those 39 patients, 7 (18%) eventually had full neurologic recovery (Table 4). These two probabilities can be multiplied, suggesting that only 5% of patients who are unconscious two days after cardiac arrest awaken and have full neurologic recovery. Multivariable predictive rules that are applicable at later times have been generated from the cooperative study on nontraumatic coma.[8]

Cerebrospinal Fluid Creatine Kinase

The time period between two and three days after cardiac arrest is critical for predicting recovery. During this period a remote possibility of full neurologic recovery still exists, but most of the patients who awaken will have some neurologic deficits and many will have severe deficits. About 80% of the patients still not awake at three days after the arrest will never awaken. An objective measure of brain damage that could be applied in this time interval would be useful. A cerebrospinal fluid (CSF) creatine kinase (CK) level seems well suited to this task. The brain is rich in the BB isoenzyme of CK, skeletal muscle in the MM isoenzyme and myocardium in the

TABLE 2 —*Relation of Score to Actual Awakening**

Score	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Patients with score who awakened, %	0	6	12	29	21	70	75	79	94	95
Grouped scores		*0,1,2*			*3,4*			*5,6,7*		*8,9*
Patients with score who awakened, %		5			24			74		95

*Modified from Longstreth et al.[5]

TABLE 3.—*Probability of Patient Ever Awaking After Out-of-Hospital Cardiac Arrest**

Days elapsed since cardiac arrest	0	0.5	1	1.5	2	3	4	7	14	21
Patients ever awaking after times specified, No.	279	157	80	56	39	21	14	12	6	3
Patients likely to awake, No.	459	281	196	165	142	115	100	66	32	16
Probability of ever awaking	.61	.56	.41	.34	.27	.18	.14	.18	.19	.19

*Modified from Longstreth et al.[2]

TABLE 4.—*Maximal Neurologic Recovery in Patients Awaking After the Times Specified**

Days elapsed since cardiac arrest	0	0.5	1	1.5	2	3	4	7	14	21
Patients ever awaking after times specified, No.	279	157	80	56	39	21	14	12	6	3
Proportion of awakening patients with										
No gross deficits	.67	.50	.26	.25	.18	.14	0	0	0	0
Cognitive deficits	.22	.32	.44	.41	.36	.24	.21	.15	0	0
Motor and cognitive deficits	.11	.18	.30	.34	.46	.62	.79	.85	1.0	1.0

*Modified from Longstreth et al.[2]

MB isoenzyme. When the brain is injured, CK-BB is released from the brain tissue into the interstitial spaces and from there into the cerebrospinal fluid. The amount released is directly proportionate to the amount of irreversibly damaged brain tissue.[24,25] Although the test has little diagnostic usefulness, it might serve as a good prognostic index of the degree of brain damage.

While the University of Washington studies were in progress, other investigators completed a series of detailed studies on CSF CK levels and cardiac arrest.[26,27] Serial determinations indicated that the CSF CK value was substantially elevated in patients who never recovered after cardiac arrest and peaked between 48 and 72 hours after the arrest. No elevation was seen at any time after cardiac arrest in patients with complete recovery. Finally, in patients with evidence of some brain dramage, intermediate values were found. A high degree of correlation between the CSF CK level and the amount of brain damage on neuropathologic examination was also found in patients who died.

Similar results were found in our patients after cardiac arrest in retrospective and prospective studies.[28] In the prospective study, results of the CSF CK determinations were withheld from physicians caring for the patients to avoid influencing decisions concerning degree of medical support. The investigator determining the degree of neurologic recovery was also unaware of the results of CSF CK determinations. We found that the CSF CK was significantly related to the neurologic outcome. Most of our incorrect predictions of awakening in patients who subsequently never awakened could be explained either by additional brain insults that followed CSF sampling, early death before neurologic recovery or early sampling of CSF CK, often less than 12 hours after arrest. Since our initial reports, we have collected about 80 additional specimens of CSF for CK isoenzyme determinations. We now suggest measuring the CK between two and three days after a cardiac arrest. To date, no patient with a CSF CK activity of 150 units per liter or greater has awakened. CSF specimens from control patients without acute brain injuries contain CK activity of less than 5 units per liter.[29] The precise cutoff that will maintain the specificity of the test at 100% remains undefined and may change as our experience with the test grows.

Doing CSF CK electrophoresis in a few of our patients has shown unusual isoenzyme patterns (Figure 1).[30] When specimens are run after adding a mild reducing agent such as dithiothreitol, activities increase due to reactivation of reversibly inactivated CSF CK. In most samples, CK-BB is the predominant isoenzyme. Other isoenzymes are sometimes seen, however. Migrating cathodal to the MM band is a band with the same mobility as that described in the literature for mitochondrial CK. Homogenized brain tissue obtained at the time of autopsy contains both CK-BB and mitochondrial CK.[31] The MM or MB isoenzymes are not found in brain tissue. Because mitochondrial CK is membrane bound, unlike CK-BB which is in the cytoplasm, and because brain tissue contains smaller amounts of it, mitochondrial CK appears in CSF only after severe brain damage. Mitochondrial CK is often found in specimens obtained from patients with brain death.

Another isoenzyme in some CSF specimens has an electrophoretic mobility similar to CK-MB in serum and the same as that described in the literature for a recombination MB. The presence of this CSF isoenzyme may represent a recombination of MM and BB.[30] When the CSF is contaminated with CK-MM from the serum, recombination with CSF CK-BB can occur to yield CK-MB. We have found CK-MB only when CK-BB and MM have had an opportunity to incubate. Consequently, in a case of a traumatic tap where the MM and BB may mix initially, we have not found MB if the specimen is immediately placed on ice and kept at 4°C until

the assay is done. Care should be taken with such contaminated specimens. The total CSF CK level may be elevated, but on electrophoresis the predominant isoenzyme may be due to CK-MM and not CK-BB. If appreciable amounts of MM are detected on electrophoresis, then CSF CK-BB is quantified by using electrophoresis or immunoinhibition techniques.

CSF CK determinations may also be useful in patients with focal brain ischemia, such as that which follows acute, ischemic stroke. As with global brain ischemia, after ischemic stroke, the CSF CK level rises, reaching a peak between two to three days after the stroke occurs.[32-35] Whether the degree of elevation correlates well with the degree of neurologic recovery has not been shown. The isoenzyme pattern might help to locate small strokes because the proportion of BB and mitochondrial CK varies in different regions of the brain.[31]

Treatment

Based on the information presented above, a prognosis for neurologic recovery can be rendered early in the clinical course of patients after cardiac arrest. Ideally, this information would identify patients with the greatest need for treatment. At present, there is no specific, effective treatment for global or focal ischemic brain injury. The duration of complete, global ischemia (from the beginning of cardiac arrest until resuscitation begins) and the duration of incomplete, global ischemia (from resuscitation until a perfusive rhythm is reestablished) are probably the major determinants of brain damage after cardiac arrest. Perhaps the outcomes determined by these insults cannot be altered, but as more is learned about the pathophysiology of brain ischemia, factors may be found that could be controlled after the insult and result in reduced brain damage.

After ischemia, calcium may have a role in the final demise of cells, including brain cells.[17,18] Calcium entry blockers have been proposed as agents to reduce ischemic brain damage,[36] but evidence for a cytoprotective effect of the calcium entry blockers in brain tissue is meager. Some investigators have even shown deleterious metabolic effects of these agents in ischemic brain.[37] Calcium entry blockers have been extensively evaluated in experiments in animals for the treatment of global brain ischemia. Many of the early investigations are difficult to interpret because of differing methods and conflicting results. In a recent study using a primate model, however, it was suggested that nimodipine may have a beneficial effect.[38] Complete, global brain ischemia was produced in pigtailed monkeys and then flow was reestablished. Five minutes after reestablishment of flow, one group was treated with parenteral administration of nimodipine and the other with placebo. Nimodipine is a new calcium entry blocker with potent and selective actions on cerebral vasculature. The animals were then observed for 96 hours and scored according to their neurologic recovery. Significantly better recovery occurred in the nimodipine-treated compared with the placebo-treated monkeys.

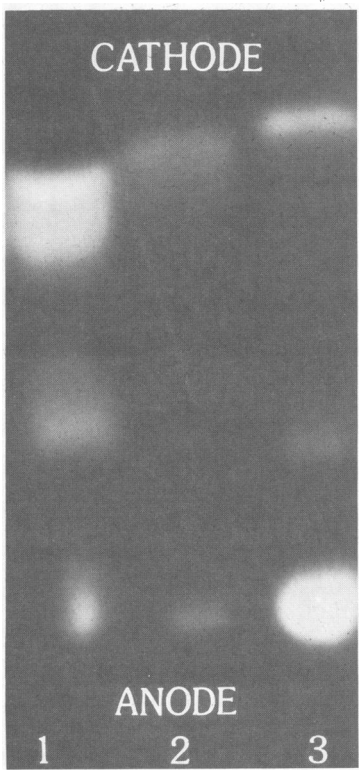

Figure 1.—Electrophoresis for creatine kinase (CK) isoenzymes shows the following: Lane 1 is control serum showing CK-MM near the cathode, CK-BB near the anode and CK-MB in between. Lane 2 is cerebrospinal fluid (CSF) from a patient after a cardiac arrest before adding a reactivating agent, dithiothreitol (DTT). Lane 3 is the same CSF specimen after the addition of DTT. Note the increase in CK-BB, the presence of mitochondrial CK migrating cathodal to the MM band and the presence of CK-MB thought due to recombination (from Chandler et al[30]).

Despite these encouraging results, some investigators have suggested that further studies are needed to confirm the beneficial effects of the calcium entry blockers in ischemic brain injury and to define better the protective mechanism.[39] In part, caution has been recommended because of the experience with barbiturates in brain ischemia. In early experiments with animals, barbiturates had also been shown to have a beneficial effect,[40] but a cooperative clinical trial with thiopental loading after cardiac arrest was done and no benefit was found.[41] When the experiments were repeated, the beneficial effects of the initial studies could no longer be shown.[42] Nevertheless, clinical trials evaluating calcium entry blockers in ischemic brain disease are already underway through an international, cooperative, National Institutes of Health-supported trial of the calcium entry blocker lidoflazine.

Calcium entry blockers have also been used in patients with acute ischemic stroke.[43,44] Nimodipine-treated patients fared significantly better than placebo-treated patients when the nimodipine was given orally in a divided dose of 120 mg a day. Both a single-blind study and a recent double-blind study have shown similar beneficial effects. Further clinical investigations of the calcium entry blockers in acute ischemic stroke are needed to confirm these promising results. Other treatments for ischemic brain disease are under active investigation, but at this time there is no known effective treatment in patients.

Decisions to Limit Medical Support

Clinicians are more often faced with decisions concerning the degree of medical support in patients who do not awaken after cardiac arrest than decisions concerning treatment. Guidelines for these decisions vary from state to state.[45] Some use a judicial approach based on case law, some use a legislative approach and others lack formal guidelines. The judicial approach adopted in Washington State is of interest. The first decision by the Washington State Supreme Court concerning medical support of unconscious and incompetent patients occurred in 1980.[46] When brain death developed in a child, his guardian felt uncomfortable with decisions concerning withdrawal of medical support. Although the child died before the ruling, the court suggested adoption of the Uniform Determination of Death Act, which recognizes both circulatory and brain death.

At the time, the justices realized that their ruling did not

apply to more difficult situations, such as one in which a permanently unconscious patient is not brain dead. Shortly after the first ruling, such a case arose.[47] Both family and physicians wanted to withdraw medical support, but hospital administrators felt uncomfortable with the decision. The court ruled in a timely fashion that the limitation was appropriate, and the patient died after being disconnected from her ventilator. With that ruling, the court set guidelines for making such decisions. The courts would be involved to varying degrees in all decisions to limit medical support. A guardian would be appointed by the courts and could then make decisions about medical support based on information supplied by a "prognosis board." Even if a close family member was deemed appropriate, this person would have to apply through the courts to be appointed guardian. The prognosis board would consist of the attending physician and two disinterested physicians who must independently conclude that there was no reasonable possibility of the patient returning to a cognitive, sapient state. The courts would be involved further only if disagreement arose.

The next case concerned a middle-aged man who had been severely handicapped all his life, never functioning at a level greater than that of a 1- to 2-year-old child. After suffering a cardiac arrest, he never awakened. His guardian felt uncomfortable with decisions concerning limiting support. A lower court ruled that a guardian could make such decisions and that it could be in the best interest of the patient to have medical support withdrawn. Support was limited and the patient died. The decision was appealed to the state's supreme court to clarify issues raised by the court in its earlier rulings. In the appeal, the supreme court partially reversed its earlier decision thereby reducing the courts' involvement in such situations.[48] It concluded that if an appropriate surrogate decision maker could be identified, there would be no need to apply to the courts to have that person appointed guardian. The need for a prognosis board and unanimous agreement on prognosis remained the same. Any disagreements concerning degree of medical support would require involvement of the courts. In the situation of a patient who had never been competent, a court-appointed guardian would be needed, but the court would not be involved further. This describes the situation based on case law that presently exists in Washington State. In most cases, there is no need to involve the courts.

Other states have adopted a legislative rather than a judicial approach. In Oregon, a case was brought before the courts in which a child was thought to be permanently unconscious. Family and physicians wanted to withdraw medical support. The court was unable to come to a decision, and an attorney was appointed as a friend of the court to collect additional information. After the child died without a court ruling, the attorney took the information that he had collected to the legislature. Eventually a "Right to Die" law was passed. It outlines a process similar to that which exists in Washington State based on case law. The prognosis board is the same, and the search for a guardian or surrogate decision maker is the same, but there is one important difference. If no surrogate decision maker can be found among family members or previously appointed guardians, then the task falls to the attending physicians. Consequently, in some circumstances the attending physician can make unilateral decisions concerning the degree of medical support. Other states have adopted different legislative approaches, including living wills and durable power of attorney.[49]

Conclusion

The clinical course and prognosis of coma after cardiac arrest have been better defined in recent years. This information may be used eventually to identify those patients who might benefit most from treatments designed to reduce brain damage following ischemic insults. At present, such treatment is not available, although several promising avenues of investigation are being explored. The use of the calcium entry blockers in global and focal brain ischemia is currently the most promising approach. More investigations in animals and in humans are needed, however, before these or any other agents become accepted treatments.

At present, though, we are more often faced with decisions concerning the limitation of medical support than with those about treatment. The guidelines to make such decisions vary from state to state and have come into existence either through rulings by the courts on individual cases or, less commonly, by legislation. In a sense, the neurologic sequelae of cardiac arrest are a result of an imperfect technology. None of these patients would have survived 20 to 30 years ago, and the sequelae did not exist. Now some patients survive and have complete neurologic recovery, but the cases of the rest raise pressing medical and ethical questions.

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